

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
19 February 2004 (19.02.2004)

PCT

(10) International Publication Number
WO 2004/014453 A1

(51) International Patent Classification⁷: **A61L 31/02**,
31/08, 31/10

(21) International Application Number:
PCT/US2003/025463

(22) International Filing Date: 13 August 2003 (13.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/403,479 13 August 2002 (13.08.2002) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

WO 2004/014453 A1

(54) Title: MEDICAL DEVICE EXHIBITING IMPROVED ADHESION BETWEEN POLYMERIC COATING AND
SUBSTRATE

(57) Abstract: Polymer-coated medical devices having improved structural integrity and drug elution profile, and related methods.
Treatment of a polymeric undercoat layer to reflow the undercoat polymer results in a substrate/coating interface with improved
adhesion.

5 MEDICAL DEVICE EXHIBITING IMPROVED ADHESION BETWEEN
POLYMERIC COATING AND SUBSTRATE

CROSS-REFERENCE TO RELATED APPLICATIONS

10 The present application claims priority to U.S. Provisional Patent
Application Serial No. 60/403,479, filed on August 13, 2002, which is
incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

15 The present invention relates to polymer-coated medical devices
having improved structural integrity, and related methods.

BACKGROUND OF THE INVENTION

 Polymeric coating of medical devices serves several functions.
20 The surfaces of implantable devices such as catheters or guide wires
must be smooth and uniform to assure introduction of such devices
without causing trauma to tissue encountered during placement. A
polymeric coating may serve as a repository for delivery of an active
agent to a subject. For many applications, polymeric coatings must be
25 as thin as possible.

 Prior art coatings suffer from limitations that include structural
failure due to cracking and delamination from the device surface. When
polymeric coatings are applied from solution, evaporation of the solvent
can cause shrinkage with consequent cracking of the coating layer.
30 Water may find its way to the interface between the coating and the
device surface, causing further structural damage. This adhesive failure
is exacerbated when the coating layers are thin. During the coating

process water or solvent molecules may also become trapped at the interface between the coating layer and the substrate, and may be responsible for the formation cavities, micropores and channels within the coating layer that can lead to premature or uncontrolled release of an active agent from the device. A "skinning" effect is sometimes observed due to the difference in evaporation rates between the solvent near the coating surface and the solvent near the substrate surface. These regions shrink at different rates, causing imperfections in the contact surface between the coating and the substrate and producing stress at the coating/substrate interface, driving delamination.

These problems result at least in part from poor adhesion of the coatings to the substrate surface. Thin polymeric coatings with improved adherence to the surface of medical devices are needed.

SUMMARY OF THE INVENTION

In one embodiment, the invention provides a medical device that includes a substrate surface, a polymeric undercoat layer that is conformably adherent to the substrate surface, and a polymeric top coat layer that is adherent to the undercoat layer. The average thickness of the undercoat layer is preferably less than about 1 micron.

Prior to the application of the top coat layer, the undercoat layer is preferably treated to reflow the undercoat polymer to cause formation of a conformable interface between the undercoat layer and the substrate surface. Reflow of the undercoat polymer is preferably accomplished by heating the undercoat layer to at least about the melt flow temperature of the undercoat polymer for a time sufficient to reflow the polymer. Optionally, the top coat layer comprises an active agent that can be either elutable or non-elutable.

In a preferred embodiment, the top coat layer includes an elutable active agent that elutes from the stent at a slower rate and for a longer duration than the active agent elutes from a comparable stent without the polymeric undercoat layer.

The top coat layer is an optional component of the medical device. Thus, in another embodiment, the polymeric top coat layer is omitted and the device includes a substrate surface and a single polymeric layer that is conformably adherent to the substrate surface.

5 Analogous to the undercoat layer in the embodiment of the device containing two or more layers, the single polymeric layer in this embodiment of the device is preferably treated to reflow the polymer to cause formation of a conformable interface between the polymer layer and the substrate surface.

10 The medical device can be an implantable device, such as a stent, or an extracorporeal device. In a particularly preferred embodiment, the medical device is a stent having a polymeric undercoat layer conformably adherent to a substrate surface of the stent and a polymeric top coat layer adherent to the undercoat layer. The undercoat
15 layer preferably includes a polyurethane, and the top coat layer preferably comprises an active agent.

The invention further provides a coating applied to a medical device that includes a polymeric undercoat layer that is conformably adherent to a substrate surface of the device, and a polymeric top coat
20 layer that is adherent to the undercoat layer. Preferably, prior to application of the top coat layer, the undercoat layer is treated to reflow the undercoat polymer to cause formation of a conformable interface between the undercoat layer and the substrate surface. Optionally, the top coat layer includes an active agent.

25 The invention further includes a method for making a medical device that includes applying an undercoat polymer to a substrate surface to form a polymeric undercoat layer, treating the polymeric undercoat layer to reflow the undercoat polymer, and, optionally, applying a top coat polymer to the undercoat layer to form a polymeric
30 top coat layer. It should be understood that in the embodiment of the device containing only a single polymer layer, the single polymer layer, being analogous to the undercoat polymer layer, is treated to reflow the polymer. Treating the undercoat layer to reflow the undercoat polymer

preferably causes the formation of a conformable interface between the undercoat layer and the substrate surface. In a preferred method, the undercoat layer is heated to at least about the melt flow temperature of the undercoat polymer for a time sufficient to reflow the polymer.

5 The invention further includes a method for delivering an active agent to a subject. The method involves contacting a delivery device with a bodily fluid, organ or tissue of a subject to deliver the active agent, wherein the delivery device includes a substrate surface, a polymeric undercoat layer conformably adherent to the substrate surface, and an
10 optional polymeric top coat layer adherent to the undercoat layer, wherein the top coat layer comprises an active agent. The method can be performed in vivo or ex vivo, depending upon whether the delivery device is an extracorporeal device or an implantable device. The active agent can be elutable or non-elutable. An elutable active agent can
15 elute from the device at a slower rate and for a longer duration than the active agent elutes from a comparable device without the polymeric undercoat layer.

 The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the
20 present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be
25 interpreted as an exclusive list.

BRIEF DESCRIPTION OF THE DRAWINGS

 Figure 1 shows cumulative release of dexamethasone from PVAC/CAB blends that were coated on the surface of SS16L shim
30 without primer treatment. The PVAC/CAB ratio was 100/0 (square), 70/30 (diamond), and 50/50 (triangle).

 Figure 2 shows cumulative release of dexamethasone from PVAC/CAB blends that were coated onto the surface of SS16L shim that

were treated with PL75D primer that had been subjected to reflow treatment. The PVAC/CAB ratio was 100/0 (square), 70/30 (diamond), and 50/50 (triangle).

5 DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The medical device of the invention is characterized by a substrate surface overlaid with a polymeric layer. This polymeric layer (termed an "undercoat" layer in devices that contain more than one polymer layer) strongly adheres to the substrate surface can serve a number of different functions. For example, it can play a role in the electric isolation or thermal isolation of the device, can provide an anti-scratch or abrasion resistant surface and/or can serve as a vehicle for chemical, physical, optical, and/or biological modification of the device surface. Optionally, this layer can be overlaid with another polymeric layer, referred to herein as a top layer or top coat layer. When the device is in use, the outermost layer (e.g., the single polymer layer or the outermost top coat layer) is in contact with a bodily fluid, organ or tissue of a subject. As a result of a novel fabrication process, the polymeric layers adhere to each other and to the substrate surface in a way that reduces or eliminates cracking and delamination of the polymeric layers. The devices thus exhibit improved structural integrity and safety compared to prior art devices. In devices having top coat layers that contain elutable active agents, the novel construction also yields a reproducible elution profile.

25 The invention is not limited by the nature of the medical device; rather, any medical device can include the polymeric undercoat layer and/or top coat layer as described herein. Thus, as used herein, the term "medical device" refers generally to any device that has surfaces that can, in the ordinary course of their use and operation, contact bodily tissue, organs or fluids such as blood. Examples of medical devices include, without limitation, stents, stent grafts, anastomotic connectors leads, needles, guide wires, catheters, sensors, surgical instruments, angioplasty balloons, wound drains, shunts, tubing, urethral inserts,

pellets, implants, pumps, vascular grafts, valves, pacemakers, and the like. A medical device can be an extracorporeal device, such as a device used during surgery, which includes, for example, a blood oxygenator, blood pump, blood sensor, or tubing used to carry blood, and the like, which contact blood which is then returned to the subject. A medical device can likewise be an implantable device such as a vascular graft, stent, electrical stimulation lead, heart valve, orthopedic device, catheter, shunt, sensor, replacement device for nucleus pulposus, cochlear or middle ear implant, intraocular lens, and the like. Implantable devices include transcutaneous devices such as drug injection ports and the like.

In general, the materials used to fabricate the medical device of the invention are biomaterials. A "biomaterial" is a material that is intended for implantation in the human body and/or contact with bodily fluids, tissues, organs and the like, and that has the physical properties such as strength, elasticity, permeability and flexibility required to function for the intended purpose. For implantable devices in particular, the materials used are preferably biocompatible materials, i.e., materials that are not overly toxic to cells or tissue and do not cause undue harm to the body.

The invention is not limited by the nature of the substrate surface that is in contact with the polymeric undercoat layer. For example, the substrate surface can be composed of ceramic, glass, metal, polymer, or any combination thereof. In embodiments having a metal substrate surface, the metal is typically iron, nickel, gold, cobalt, copper, chrome, molybdenum, titanium, tantalum, aluminum, silver, platinum, carbon, and alloys thereof. A preferred metal is stainless steel, a nickel titanium alloy, such as NITINOL, or a cobalt chrome alloy, such as NP35N.

Preferably, the substrate surface is not activated or functionalized prior to application of the undercoat layer, although in some embodiments, pretreatment of the substrate surface may be desirable to promote adhesion. Typically, the substrate surface is cleaned with an appropriate solvent to remove surface contamination. The substrate

surface can also be cleaned with other methods, such as plasma treatment and thermal treatment.

The polymeric undercoat layer (or single layer in the embodiment of the device that contains only one polymer layer) can adhere to the substrate surface by either covalent or non-covalent interactions. Non-covalent interactions include ionic interactions, hydrogen bonding, dipole interactions, hydrophobic interactions and van der Waals interactions, for example. The undercoat layer can be cross-linked or non-cross-linked.

The polymer that is adherent to the substrate surface (generally referred to herein for ease of reference as the undercoat polymer, although it is to be understood that the undercoat layer may be the only polymer layer on the device) is preferably a polymer that contains polar groups, however polymers lacking such groups such as styrene or olefin polymers may also be used. Polar groups include hydroxyl, amine, carboxyl, ether, ester, sulfoxide, sulfone, urea, amide, urethane, thiol, carbonate, acetal, carboxylic acid, alkyl halide and combinations thereof. Preferred polymers include polyurethanes, polyesters, polycarbonates, polymethacrylates, polysulfones, polyimides, polyamides, epoxies, polyacetals, vinyl polymers, and blends or copolymers thereof. These polar functional groups facilitate non-covalent bonding with the substrate surface as well as with the optional top coat layer. The undercoat polymer is preferably not a hydrogel.

A particularly preferred undercoat layer consists essentially of a polyurethane. Such a preferred undercoat layer includes a polymer blend that contains polymers other than polyurethane but only in amounts so small that they do not appreciably affect the durometer, durability, adhesive properties, structural integrity and elasticity of the undercoat layer compared to an undercoat layer that is exclusively polyurethane. A particularly preferred undercoat layer includes polyurethane having a Shore durometer hardness of between about 50A to 90D, more preferably about 55D to about 85D, most preferably about 75D. The hardness numbers are derived from the Shore scale, with the

A scale being used for softer and the D scale being used for harder materials.

Particularly preferred polymers for use in forming the undercoat layer include polyurethanes available from Thermedics, Inc., Woburn, MA, including polymers marketed under the tradenames TECOPHILIC, TECOPLAST, TECOTHANE, CARBOTHANE, and TECOFLEX. Other preferred polymers include the PELLETHANE and ISOPLAST series available from Dow Chemical Co., Midland MI, especially PELLETHANE 75D; ELASTHANE, PURSIL, CARBOSIL, BIONATE and BIOSPAN, available from the Polymer Technology Group, Inc., Berkeley, CA; ESTANE, available from Noveon, Inc., Cleveland, OH; ELAST-EON, available from AorTech Biomaterials, Frenchs Forest, NSW, Australia; TEXIN, available from Bayer Corporation, Pittsburgh, PA, and other commercially available polymers such as those available from Huntsman Corporation, Salt Lake City, UT.

The invention is not limited by the process used to apply the undercoat polymer to the substrate surface, except that polymerization of the undercoat polymer preferably takes place, in whole or in part, prior to application of the polymer to the substrate surface. Optionally, curing or completion of cross-linking takes place after application of the polymer. Typically, the undercoat polymer is applied to the substrate surface using a solution process, powder coating, melt extrusion, a Langmuir-Blodgett process, gas plasma deposition, chemical vapor deposition or physical vapor deposition. Examples of solution processes include spray coating, dip coating and spin coating. Typical solvents for use in a solution process include tetrahydrofuran (THF), ethanol, methanol, ethylacetate, dimethylformamide (DMF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dioxane, N-methyl pyrrolidone, chloroform, hexane, heptane, cyclohexane, toluene, formic acid, acetic acid, and/or dichloromethane. Single coats or multiple thin coats of the undercoat polymer can be applied. In a preferred embodiment of the device which includes one or more top coat layers, the undercoat layer is at least partially miscible with the top coat layer.

The coatings or films applied to the substrate surface in accordance with the invention are preferably very thin. The average thickness of the undercoat layer is preferably less than about 2 microns, more preferably less than about 1 micron, even more preferably less than about 0.5 micron, and most preferably less than about 0.1 micron (100 nm). Spin coating can be used to form an undercoat layer having a thickness from about 10 nm to about 500nm, with an average thickness of less than about 100 nm readily attained; when a Langmuir-Blodgett process is used, the average thickness can be further reduced to less than about 10 nm.

The invention is not limited by the nature of the optional polymeric top coat layer that is applied to the undercoat layer, or by the process used to apply the top coat polymer to the undercoat layer. The top coat polymer can be selected to render the top coat layer erodable or non-erodable (i.e., biostable), depending on the intended medical application. Single coats or multiple thin coats of the top coat polymer may be applied. Two or more different top coats may be applied. Exemplary polymers and application processes are as described for the undercoat layer, but are not intended to be limited thereby. The top coat polymer can be polymerized, in whole or in part, either before being applied to the device or after being applied to the device. Optionally, curing or completion of cross-linking takes place after application of the top coat layer to the device.

Examples of polymers and polymer blends that can be used to form the undercoat and/or optional top coat layers are described, for example, in U.S. Provisional Patent Application Serial No. 60/403,352, filed on August 13, 2002, and in U.S. Patent Application Serial No. _____, filed on August 13, 2003.

Optionally, the top coat layer has an active agent incorporated therein (e.g., dispersed or dissolved), preferably a therapeutic agent. If multiple top coat layers are used, the active agent may be incorporated into one or more of those layers. In other embodiments, an active agent may, additionally or alternatively, be incorporated into the undercoat

layer (or the single polymer layer, in a device having only one polymer layer).

As used herein, an "active agent" is one that produces a local or systemic effect in a subject (e.g., an animal). Typically, it is a pharmacologically active substance. The term is used to encompass any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or in the enhancement of desirable physical or mental development and conditions in a subject. The term "subject" used herein is taken to include humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice, birds, reptiles, fish, insects, arachnids, protists (e.g., protozoa), and prokaryotic bacteria. Preferably, the subject is a human or other mammal.

Active agents can be synthetic or naturally occurring and include, without limitation, organic and inorganic chemical agents, polypeptides (which is used herein to encompass a polymer of L- or D- amino acids of any length including peptides, oligopeptides, proteins, enzymes, hormones, etc.), polynucleotides (which is used herein to encompass a polymer of nucleic acids of any length including oligonucleotides, single- and double-stranded DNA, single- and double-stranded RNA, DNA/RNA chimeras, etc.), saccharides (e.g., mono-, di-, poly-saccharides, and mucopolysaccharides), vitamins, viral agents, and other living material, radionuclides, and the like. Examples include antithrombogenic and anticoagulant agents such as heparin, coumadin, coumarin, protamine, and hirudin; antimicrobial agents such as antibiotics; antineoplastic agents and anti-proliferative agents such as etoposide and podophylotoxin; antiplatelet agents including aspirin and dipyridamole; antimitotics (cytotoxic agents) and antimetabolites such as methotrexate, colchicine, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin nucleic acids; antidiabetic such as rosiglitazone maleate; and anti-inflammatory agents. Anti-inflammatory agents for use in the present invention include glucocorticoids, their salts, and derivatives thereof, such as cortisol, cortisone, fludrocortisone, Prednisone, Prednisolone, 6 α -

methylprednisolone, triamcinolone, betamethasone, dexamethasone, beclomethasone, aclomethasone, amcinonide, clebethasol and clocortolone.

5 In some embodiments, the active agent is elutable from the top coat layer; in other embodiments, the active agent is affixed to or sequestered within the top coat layer. In a preferred embodiment, the active agent is present in a higher concentration in the top coat layer than the undercoat layer.

10 When a stent or other vascular prosthesis is implanted into a subject, restenosis is often observed during the period beginning shortly after injury to about four to six months later; thus for embodiments of the invention that include stents, the generalized elution rates contemplated are such that the active agent, such as a drug, may start to be released immediately after the prosthesis is secured to the lumen wall to lessen
15 cell proliferation. The active agent may continue to elute for days, weeks or months, as desired.

The coating layers are applied to the substrate surface using a novel process that yields a device having improved structural integrity, particularly when exposed to fluids. Prior to application of a top coat
20 layer, the undercoat layer is treated to reflow the undercoat polymer. The device fabrication process thus involves first applying an undercoat polymer to a substrate surface to form the polymeric undercoat layer, followed by treating the polymeric undercoat layer to reflow the undercoat polymer, followed, in embodiments of the device that contain
25 two or more polymer layers, by applying a top coat polymer to the reformed undercoat layer to form the polymeric top coat layer.

Treating the polymeric undercoat layer to reflow the undercoat polymer causes the formation of a "conformable interface" between the undercoat layer and the substrate surface, and also provides a better
30 contact surface for the top coat layer when subsequently applied. The undercoat polymer reflows to fill cavities and imperfections in the substrate surface, thereby effectively increasing the contact area and interactions between the undercoat polymer and the substrate surface.

Reflow of the polymer also forces out solvent and/or water molecules that may have been trapped at the interface during application of the undercoat polymer. The interface between the undercoat layer and the substrate surface that results from the reflow process, which exhibits
5 more robust adhesion properties, is referred to herein a "conformable interface." Analogously, after reflow treatment, the polymeric undercoat layer is referred to as "conformably adherent" to the substrate surface. At the interface between the undercoat layer and the substrate surface, the undercoat polymer matches the contours of the substrate surface to
10 exclude water and solvent molecules and maximize interfacial contact.

Reflow of the undercoat polymer can be accomplished in any convenient manner. For example, reflow can be achieved by using thermal treatment, infrared treatment, microwave treatment, RF treatment, mechanical treatment such as compression or shearing, or
15 solvent treatment.

Preferably, the undercoat layer is heated to reflow the undercoat polymer. The undercoat layer is heated to a temperature that is at least as high as the "melt flow temperature" of the undercoat polymer for the time selected to reflow the polymer.

20 A polymer may exhibit either or both a T_g (the melt temperature for a glass) and a T_m (the melt temperature of a crystal). If a polymer is semi-crystalline, it has both a T_m and a T_g . T_m is greater than T_g . The melt flow temperature for a polymer is above the T_g and/or the T_m of the polymer. If a polymer is amorphous and has no crystallinity, it has only a
25 T_g . The melt flow temperature of amorphous polymers is above the T_g . T_g 's can be determined by measuring the mechanical properties, thermal properties, electric properties, etc. as a function of temperature.

It is well-established that physical properties of polymers, such as viscosity, vary with temperature. When the temperature is below the T_g
30 of a polymer, the polymer is said to be in a "glassy state." In a glassy state the polymer is rigid, with a modulus typically within the GPa range. A polymer in a glassy state does not significantly "flow" within a long time frame (years). When the temperature is increased to above the T_g

of polymer, the polymer is said to be in a rubbery state. The polymer's modulus in a rubbery state is typically within the MPa range. A polymer in a rubbery state does not significantly flow within a short time frame (hours to days) but may flow on a longer (years) scale. If the temperature is further increased, the polymer chains (i.e., macromolecules) become able to move on a scale of minutes. At this point, the polymer is said to be in a "liquid flow state." The polymer molecules are now able to flow, i.e., deform permanently like a liquid, rather than reversibly deform as in a rubber state. In a liquid flow state, the polymer molecules begin to translocate on the order of minutes, with a consequent movement of their center of mass.

For any time period selected for thermal treatment, the temperature at which the polymer will enter the liquid flow state and reflow during that time period (i.e., the "melt flow temperature") is the preferred minimum temperature that is used to reflow the polymer. It should be clear from the above discussion that melt flow temperature and time are inversely related; the lower the temperature selected for thermal treatment, the longer the time period during which the polymer must be heated in order to cause polymer reflow.

It is typically convenient to reflow the polymer within a period of about 5 to 10 minutes (i.e., on the minute scale). To reflow a polyurethane such as PELLETHANE 75D during this time period, a temperature of about 215°C to about 220°C can be used. On this time scale, reflow of most of the polymers useful as undercoat polymers can be accomplished using a melt flow temperature above about 200°C; for many of them a temperature above about 180°C is sufficient. The melt flow temperature is also a function of molecular weight; i.e., for the same type of polymer and same reflow time, the higher the molecular weight, the higher the melt flow temperature. A skilled artisan can readily determine the melt flow temperature and reflow time for any particular polymer by conducting a few simple melt experiments at different temperatures for the desired time interval.

Typically 1 to 10 minutes is the time period used to reflow the polymer using a thermal treatment in accordance with the invention. It should be cautioned that excessive time at high temperatures is to be avoided as the polymer can begin to degrade.

5 Surprisingly, when an elutable active agent is included in the top coat layer, the medical device of the invention exhibits improved release characteristics. In particular, the active agent elutes from the device at a slower rate and for a longer duration than it elutes from a comparable device lacking the polymeric undercoat layer. In addition, the elution
10 profile is more reproducible. Without being bound by theory, it is believed that the kinetics of elution are affected by the primer coat. Cracking and delamination are reduced, eliminating routes for premature release of the active agent. It is believed that the agent elutes more
15 uniformly from the surface of the top coat in contact with the body fluid, organ or tissue (i.e., the interface between the device and the tissue, organ or fluid) as intended, rather than from the undercoat/substrate interface due to delamination or through cracks in the coating surface.

EXAMPLES

20

The present invention is illustrated by the following examples. It is to be understood that the particular examples, materials, amounts, and procedures are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein.

25

Example I.

Untreated poly(etherurethane) coating applied to a metal surface

Poly(etherurethane) (PELLETHANE) 75D (Dow Chemical Co.,
30 Midland, MI) was cast from 1 wt% tetrahydrofuran (THF) solution to a bare stainless steel (316L) shim surface. Specifically, PELLETHANE 75D was dried overnight at 70°C under reduced pressure, then melted and pressed between two hot plates at 230°C for 5-10 minutes. After

the films were cooled in air, a tetrahydrofuran (THF) solution with 1 wt-% of PELLETHANE 75D was made by dissolving the films in anhydrous THF at about 25°C by stirring with a magnetic bar overnight. The solution was coated onto a bare stainless steel (316L) shim surface that
5 was cleaned by rinsing with THF. The coating was dried in a moisture free environment by purging with N₂ gas.

The coated shim was immersed in phosphate buffered saline solution (PBS, potassium phosphate monobasic (NF tested), 0.144 g/L, sodium chloride (USP tested), 9 g/L, and sodium phosphate dibasic
10 (USP tested) 0.795 g/L, pH = 7.0 to 7.2 at 37°C, purchased from HyClone, Logan, UT) and shaken periodically by hand. After about 5 minutes, the coating delaminated from the shim. This demonstrated that without primer pretreatment, the adhesion between the polymer coating and stainless steel was poor in PBS.

15

Example II.

Thermal treatment of poly(etherurethane) coating applied to a metal surface

20 The PELLETHANE-coated 316L shim made in Example I was thermally pretreated by heating it at 215°C to 220 °C for 5 to 10 minutes in air or, preferably, inert gas (i.e., N₂). Then the treated shim was cooled to room temperature and was immersed in PBS for more than 1 month. The coating strongly adhered to the metal surface and did not
25 delaminate during that time period. This thermally treated PELLETHANE 75D coating is referred to in the following examples as "PELLETHANE primer," and surfaces that have been coated with a primer (whether PELLETHANE or another primer) then thermally treated as in this example are referred to as "primed surfaces." Primed surfaces
30 that have not been thermally treated (such as in Example IV) will be specifically indicated.

Example III.

Poly(caprolactone) (PCL) coating applied to a metal surface

5 PCL was coated from a 1 wt% THF solution to a bare stainless steel (316L) shim surface. The coating was dried in a moisture free environment by purging with N₂ gas. The coated shim was immersed in PBS solution and periodically shaken by hand. The PCL film delaminated from substrate within about 2 minutes. The adhesion between the 316L shim and PCL was poor.

10

Example IV.

PCL coating applied to a metal surface primed but not thermally treated

15 PELLETHANE (PL75D) was coated onto the surface of a 316L shim without thermal treatment. PCL was then coated from 1wt% of THF solution onto the primed metal surface. The coating was dried in a moisture free environment by purging with N₂ gas. The coated shim was immersed in PBS solution at room temperature and periodically shaken by hand. The PCL film delaminated from substrate within about 20 2 minutes. The non-thermally treated PL75D layer did not promote the adhesion between PCL and the 316L shim.

Example V.

PCL coating applied to a primed metal surface (PELLETHANE)

25

PELLETHANE (PL75D) was coated onto the surface of a 316L shim and thermally treated as in Example II (e.g., 215 - 220 °C for 5 to 10 minutes). PCL was then coated from 1wt% of THF solution onto the primed metal surface. The coating was dried in a moisture free 30 environment by purging with N₂ gas. The coated shim was immersed in PBS solution and periodically shaken by hand for about 5 minutes. The PCL film did not delaminate from substrate. Then the sample was left in PBS at room temperature for 12 days. No delamination was

observed. The thermally treated primer thus promoted the adhesion between PCL and the 316L shim.

Example VI.

5 Drug-loaded poly(vinyl acetate) (PVAC)/ cellulose acetate butyrate (CAB) blend applied to a primed metal surface (PELLETHANE primer)

Various PVAC/CAB blends loaded with about 10 wt% of dexamethasone were coated onto PELLETHANE primer treated
10 (Example II) and nontreated 316L shims and the samples were dried. The coatings having a CAB fraction more than 30 wt% delaminated from the nontreated shims within the first two hours of immersion in PBS at 37 °C. However, no delamination was observed from the treated surfaces even after 1 month of immersion in PBS at the same temperature.

15

Example VII.

PVAC/CAB blends applied to primed stent surface (PELLETHANE primer)

20 A PVAC/CAB (50/50) blend was coated onto PELLETHANE primer treated (as in Example II) and nontreated 316L stents (S7, Medtronic AVE, Santa Rosa, CA), and the samples were dried. A scratch test showed that the coating in the primer treated cases adhered to the treated stents much more strongly than the un-treated stents. The
25 average thickness of the primers on the stents was about 0.4 to 1.0 microns.

Example VIII.

Drug (Dexamethasone)-loaded poly(carbonate urethane)/polycarbonate (PCU/PC) blends applied to a primed metal surface (PELLETHANE primer)

5

Various PCU/PC blends loaded with about 10 wt% of dexamethasone were coated onto PELLETHANE primer treated (Example II) and nontreated 316L shims. Most of the coatings delaminated from the untreated shims within the first 2 days of immersion in PBS and all of them delaminated after 6 more days. However, there was essentially no delamination from the treated shims under the same conditions after at least 4 weeks.

10

Example IX.

PCU/PC blends applied to a primed metal stent surface (PELLETHANE primer)

15

PCU/PC blends (100/0, 95/5, and 50/50) were coated onto 316L stents with and without PELLETHANE primer (0.7 – 1.2 micron thick). A scratch test showed that the coatings in the primer-treated stents adhered more strongly than that in the untreated stents.

20

Example X.

Drug-loaded PELLETHANE 75D (PL75D)/TECOPLAST blend applied to a primed metal stent surface (PELLETHANE primer)

25

PL75D/TECOPLAST blends loaded with a low molecular weight, hydrophobic active agent were coated onto PELLETHANE primer treated stents (Example II) from a THF solution. The coatings were durable and no delamination was observed during immersion in PBS at 37 °C for at least 14 days.

30

Example XI.

Polycarbonate (PC) coating applied to a primed metal surface
(poly(carbonate urethane) primer)

5 An 316L metal shim was pretreated with poly(carbonate
urethane) primer coating using the procedure described in Example II for
PELLETHANE 75D primer. Polycarbonate was coated onto the primed
surface, and also onto shims that were not pretreated. The coating
adhered to the pretreated shim very well and no delamination was
10 observed during immersion in PBS at room temperature for at least 4
weeks. If the shims were not pretreated with a PCU primer (or other
primer), the PC film delaminated within 5 – 10 minutes of immersion in
PBS.

15 **Example XII.**

Drug-loaded TECOPHILIC/poly(vinyl acetate-co-vinyl pyrrolidone) (PVP-VA) coating applied to a primed metal stent surface (TECOPHILIC primer)

20 A 316L stent was pretreated with TECOPHILIC (polyethylene oxide urethane) (TCPL) primer using the same procedure as that for the PELLETHANE primer in Example II. PVP-VA was from Sigma-Aldrich Chemical Company, Milwaukee, WI. TCPL/PVP-VA loaded with RESTEN NG (7,000 g/mol molecular weight and water-soluble antisense
25 oligonucleotide. AVI Biopharma, Corvallis, Oregon) was coated onto the primed surface. The stents were subjected to a durability test during which they were mounted on a balloon catheter (Medtronic AVE, Santa Rosa, CA) and passed down a PBS-filled 2 mm (i.d.) J-bended catheter (Medtronic AVE, Santa Rosa, CA), then radially expanded in PBS. The
30 stents were viewed using optical microscopy and, in some instances, scanning electron microscopy (SEM). No delamination was observed.

Example XIII.

Polycarbonate coating applied to a primed metal surface (TECOPLAST primer)

5 A 316L shim was pretreated with TECOPLAST (polyether urethane) (TCPT) primer using the same procedure as that for the PELLETHANE primer in Example II. Polycarbonate (PC) was coated onto the primed surface. The PC film adhered to the shim very well and no delamination was observed after the coating immersed in PBS for at
10 least 1 month.

Example XIV.

Improved drug release properties from poly(vinyl acetate) (PVAC)/
cellulose acetate butyrate (CAB) blend coating applied to a primed metal
15 surface (PELLETHANE primer)

Mixtures of PVAC and CAB with weight ratios varying from 100/0 to 50/50, each loaded with about 10 wt% of dexamethasone. The solutions were cast the solutions onto the surface of bare SS16L shims (control) and PL75D primer treated SS16L shims (as in Example II).
20 After the samples completely dried under nitrogen gas, dexamethasone dissolution tests were conducted in PBS solution (3 mL) at 37° C. During testing, the vials were shaken at a rate of about 10 times per minute. The dissolution solution for each sample was refreshed at various times. The eluted dexamethasone was measured with a UV-Vis spectroscopy (HP 4152A). The cumulative drug release per area of sample size was plotted as a function of square root of time.
25 Theoretically, cumulative release per area should be a linear function of square root of time at the early stage of release. Then the release rate decreases exponentially, approaching zero at infinitely long time.
30

For the samples on the bare shims, the release curves are plotted in Figure 1. For each blend (PVAC/CAB 100/0, 70/30 and 50/50), the elution profile observed during the initial elution period differed from the

expected linear trend (shown as dashed lines in Fig. 1). It is believed that this deviation is attributable to delamination of the coating from the shim. Delamination causes the drug to release from the device prematurely, and therefore increases the rate of drug delivery.

5 Release curves for sample on the primer treated shim are shown in Figure 2. The observed cumulative release for each different PVAC/CAB blend was a linear function of the square root of time at early stage then slowed down, as would be expected from theory. Therefore, the primer improved the release properties of drug from the thin polymer
10 films.

 The complete disclosures of all patents, patent applications including provisional patent applications, and publications, and electronically available material cited herein are incorporated by
15 reference. The foregoing detailed description and examples have been provided for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described; many variations will be apparent to one skilled in the art and are intended to be included within the invention
20 defined by the claims.

WHAT IS CLAIMED IS:

1. A medical device comprising:
 - a substrate surface;
 - 5 a polymeric undercoat layer conformably adherent to the substrate surface; and
 - a polymeric top coat layer adherent to the undercoat layer.
2. The medical device of claim 1 wherein, prior to application of the top
10 coat layer, the undercoat layer is treated to reflow the undercoat polymer to cause formation of a conformable interface between the undercoat layer and the substrate surface.
3. The medical device of claim 1 wherein the polymeric undercoat
15 comprises polar groups selected from the group consisting of hydroxyl, amine, carboxyl, ether, ester, sulfoxide, sulfone, urea, amide, urethane, thiol, carbonate, acetal, carboxylic acid, alkyl halide and combinations thereof.
- 20 4. The medical device of claim 1 wherein the average thickness of the undercoat layer is less than about 1 micron.
5. The medical device of claim 1 wherein the polymer undercoat layer is applied to the substrate surface using a technique selected from the
25 group consisting of a solution process, powder coating, melt extrusion, vapor deposition, or a Langmuir-Blodgett process.
6. The medical device of claim 5 wherein the solution process is a spray coat, a dip coat, or a spin coat.
- 30 7. The medical device of claim 1 wherein the polymer undercoat layer comprises at least one polymer selected from the group consisting of a polyurethane, a polyester, a polycarbonate, a polymethacrylate, a

polysulfone, a polyimide, a polyamide, a linear epoxy, a polyacetal, a vinyl polymer, and any blend or copolymer thereof.

8. The medical device of claim 1 wherein the polymer undercoat layer
5 comprises a polyurethane.

9. The medical device of claim 1 wherein the undercoat layer adheres to the substrate surface by way of non-covalent interactions.

10. The medical device of claim 1 wherein the undercoat layer adheres
10 to the substrate surface by way of covalent interactions.

11. The medical device of claim 1 wherein the undercoat layer does not
15 comprise a hydrogel.

12. The medical device of claim 1 wherein the undercoat layer is not
cross-linked.

13. The medical device of claim 1 wherein the undercoat layer is
20 polymerized prior to application to the substrate surface.

14. The medical device of claim 2 wherein treating the undercoat layer
to reflow the undercoat polymer comprises using a technique selected
from the group consisting of thermal treatment, infrared treatment,
25 microwave treatment, RF treatment, mechanical treatment and solvent
treatment.

15. The medical device of claim 2 wherein treating the undercoat layer
to reflow the undercoat polymer comprises heating the undercoat layer
to at least about the melt flow temperature of the undercoat polymer for
30 a time sufficient to reflow the polymer.

16. The medical device of claim 1 wherein the top coat layer comprises an active agent.
17. The medical device of claim 16 wherein the top coat layer
5 comprises an elutable active agent that elutes from the device at a slower rate and for a longer duration than the active agent elutes from a comparable device without the polymeric undercoat layer.
18. The medical device of claim 16 wherein the active agent is present
10 in a higher concentration in the top coat layer than the undercoat layer.
19. The medical device of claim 16 wherein the active agent is selected from the group consisting of an anti-thrombogenic agent, an anticoagulant agent, an anti-microbial agent, an anti-neoplastic agent,
15 an anti-proliferative agent, an antiplatelet agent, an antimetabolite, and an anti-inflammatory agent.
20. The medical device of claim 1 wherein the substrate surface
20 comprises a material selected from the group consisting of ceramic, glass, metal and a polymer.
21. The medical device of claim 20 wherein the metal is selected from the group consisting iron, nickel, gold, cobalt, copper, chrome, molybdenum, titanium, tantalum, aluminum, silver, platinum, carbon, and
25 alloys thereof.
22. The medical device of claim 21 wherein the alloy is stainless steel, a nickel titanium alloy, or a cobalt chrome alloy.
23. The medical device of claim 1 wherein the substrate surface is not
30 activated or functionalized prior to application of the undercoat layer.
24. The medical device of claim 1 which is an implantable device.

25. The medical device of claim 1 which is an extracorporeal device.
26. The medical device of claim 1 selected from the group consisting of
5 a stent, stent graft, anastomatic connector, lead, needle, guide wire,
catheter, sensor, surgical instrument, angioplasty balloon, wound drain,
shunt, tubing, urethral insert, pellet, implant, blood oxygenator, pump,
vascular graft, valve, pacemaker, orthopedic device, replacement device
for nucleus pulposus, and intraocular lense.
- 10 27. The medical device of claim 1 which is a stent.
28. A stent comprising:
at least one substrate surface;
15 a polymeric undercoat layer conformably adherent to the
substrate surface, said undercoat layer comprising a polyurethane; and
a polymeric top coat layer adherent to the undercoat layer, said
top coat layer comprising an active agent.
- 20 29. The stent of claim 28 wherein, prior to application of the top coat
layer, the undercoat layer is treated to reflow the undercoat polymer to
cause formation of a conformable interface between the undercoat layer
and the substrate surface.
- 25 30. The stent of claim 28 wherein the top coat layer comprises an
elutable active agent that elutes from the stent at a slower rate and for a
longer duration than the active agent elutes from a comparable stent
without the polymeric undercoat layer.
- 30 31. In a delivery device having a substrate surface, a polymeric
undercoat layer adherent to the substrate surface, and a polymeric top
coat layer adherent to the undercoat layer, wherein the top coat layer
comprises an active agent, the improvement comprising a conformable

interface between the undercoat layer and the substrate surface formed by treating the polymeric undercoat layer to reflow the undercoat polymer prior to application of the top coat layer.

5 32. In a stent having a substrate surface, a polymeric undercoat layer
adherent to the substrate surface, and a polymeric top coat layer
adherent to the undercoat layer, wherein the top coat layer comprises an
active agent, the improvement comprising a conformable interface
10 between the undercoat layer and the substrate surface formed by
treating the polymeric undercoat layer to reflow the undercoat polymer
prior to application of the top coat layer, wherein the undercoat layer
comprises polyurethane.

33. A medical device prepared by the process of:
15 applying an undercoat polymer to the substrate surface to form
the polymeric undercoat layer;
treating the polymeric undercoat layer to reflow the undercoat
polymer;
applying a top coat polymer to the undercoat layer to form the
20 polymeric top coat layer.

34. The medical device of claim 33 wherein treating the polymeric
undercoat layer to reflow the undercoat polymer causes the formation of
a conformable interface between the undercoat layer and the substrate
25 surface.

35. The medical device of claim 33 wherein treating the polymeric
undercoat layer to reflow the undercoat polymer comprises heating the
polymeric undercoat layer to at least about the melt flow temperature of
30 the undercoat polymer for a time period sufficient to reflow the undercoat
polymer.

36. The medical device according to claim 33 wherein the undercoat layer comprises polyurethane.

37. The medical device of claim 33 wherein the top coat layer
5 comprises an active agent.

38. The medical device of claim 33 wherein the top coat layer comprises an elutable active agent that elutes from the device at a slower rate and for a longer duration than the active agent elutes from a
10 comparable device without the polymeric undercoat layer.

39. The medical device of claim 33 which is a stent.

40. A medical device comprising:
15 a substrate surface;
a polymeric undercoat layer adherent to the substrate surface;
and
a polymeric top coat layer adherent to the undercoat layer, said top coat layer comprising an elutable active agent, wherein the active
20 agent elutes from the stent at a slower rate and for a longer duration than the active agent elutes from a comparable stent without the polymeric undercoat layer.

41. The medical device of claim 40 which is a stent.
25

42. A medical device comprising:
a substrate surface;
a polymeric undercoat layer comprising a polyurethane, wherein the polymeric undercoat layer is adherent to the substrate surface and
30 has an average thickness of less than about 1 micron; and
a polymeric top coat layer adherent to the undercoat layer.

43. The medical device of claim 42 wherein the top coat layer comprises an active agent.

44. A stent comprising:

- 5 a substrate surface;
 a polyurethane undercoat layer adherent to the substrate surface,
wherein the average thickness of the undercoat layer is less than about
1 micron; and
 a polymeric top coat layer adherent to the undercoat layer, said
10 top coat layer comprising an active agent.

45. A coating applied to a medical device comprising a substrate surface, the coating comprising:

- 15 a polymeric undercoat layer conformably adherent to the
substrate surface; and
 a polymeric top coat layer adherent to the undercoat layer.

46. The coating of claim 45 wherein, prior to application of the top coat
20 layer, the undercoat layer is treated to reflow the undercoat polymer to
cause formation of a conformable interface between the undercoat layer
and the substrate surface.

47. The coating of claim 46 wherein treating the undercoat layer
25 comprises heating the undercoat layer.

48. The coating of claim 45 wherein the top coat layer comprises an
active agent.

30 49. The coating of claim 45 wherein the undercoat layer comprises a
polyurethane.

50. A method for making a medical device comprising:
 applying an undercoat polymer to a substrate surface to form a
polymeric undercoat layer;
 treating the polymeric undercoat layer to reflow the undercoat
5 polymer;
 applying a top coat polymer to the undercoat layer to form a
polymeric top coat layer.
51. The method of claim 50 wherein treating the undercoat layer to
10 reflow the undercoat polymer causes formation of a conformable
interface between the undercoat layer and the substrate surface.
52. The method of claim 50 wherein treating the undercoat layer to
reflow the undercoat polymer comprises using a technique selected from
15 the group consisting of thermal treatment, infrared treatment, microwave
treatment, RF treatment, mechanical treatment and solvent treatment.
53. The method of claim 50 wherein treating the undercoat layer to
reflow the undercoat polymer comprises heating the undercoat layer to
20 at least about the melt flow temperature of the undercoat polymer for a
time sufficient to reflow the polymer.
54. The method of claim 50 wherein treating the undercoat layer to
reflow the undercoat polymer comprises heating the undercoat layer to
25 at least about 200°C for a time period sufficient to reflow the undercoat
polymer.
55. The method of claim 50 wherein the undercoat polymer comprises a
polyurethane.
30
56. The method of claim 50 wherein the substrate surface comprises a
material selected from the group consisting of ceramic, glass, metal and
a polymer.

57. The method of claim 50 wherein the top coat layer comprises an active agent.

58. The method of claim 50 wherein the top coat layer comprises an elutable active agent that elutes from the device at a slower rate and for a longer duration than the active agent elutes from a comparable device without the polymeric undercoat layer.

59. The method of claim 50 wherein the device is a stent.

60. A method for delivering an active agent to a subject comprising:
providing a delivery device comprising
a substrate surface;
a polymeric undercoat layer conformably adherent to the substrate surface; and
a polymeric top coat layer adherent to the undercoat layer, wherein the top coat layer comprises an active agent; and
contacting the delivery device with a bodily fluid, organ or tissue of a subject.

61. The method of claim 60 wherein the delivery device is an extracorporeal device.

62. The method of claim 60 wherein the delivery device is an implantable device.

63. The method of claim 60 wherein the delivery device is a stent.

64. The method of claim 60 wherein the undercoat layer comprises a polyurethane.

65. The method of claim 60 wherein the top coat layer comprises an elutable active agent that elutes from the device at a slower rate and for

a longer duration than the active agent elutes from a comparable device without the polymeric undercoat layer.

66. A method for delivering an active agent to a subject comprising:
- 5 providing a delivery device comprising
- a substrate surface;
- a polymeric undercoat layer adherent to the substrate surface; and
- a polymeric top coat layer adherent to the undercoat layer,
- 10 wherein the top coat layer comprises an elutable active agent that elutes from the device at a slower rate and for a longer duration than the active agent elutes from a comparable device without the polymeric undercoat layer; and
- contacting the delivery device with a bodily fluid, organ or tissue
- 15 of a subject.

67. The method of claim 66 wherein the delivery device is an extracorporeal device.

- 20 68. The method of claim 66 wherein the delivery device is an implantable device.

69. The method of claim 66 wherein the delivery device is a stent.

- 25 70. The method of claim 66 wherein the undercoat layer comprises a polyurethane.

71. A medical device comprising:
- a substrate surface; and
- 30 a polymer layer conformably adherent to the substrate surface.

72. A medical device prepared by the process of:
- applying a polymer layer to a substrate surface; and

treating the polymer layer to reflow the polymer;
to form a medical device comprising a substrate surface and a
polymer layer conformably adherent thereto.

5 73. The medical device of claim 72 wherein treating the polymer layer to
reflow the polymer comprises using a technique selected from the group
consisting of thermal treatment, infrared treatment, microwave
treatment, RF treatment, mechanical treatment and solvent treatment.

10 74. The medical device of claim 72 wherein treating the polymer layer to
reflow the polymer comprises heating the polymer layer to at least about
the melt flow temperature of the polymer for a time sufficient to reflow
the polymer.

15 75. The medical device of claim 72 wherein the polymer layer
comprises an active agent.

76. A method for making a medical device comprising:
applying an polymer to a substrate surface to form a polymeric
20 layer; and
treating the polymeric layer to reflow the polymer.

77. The method of claim 76 wherein treating the polymeric layer to
reflow the polymer causes formation of a conformable interface between
25 the polymeric layer and the substrate surface.

78. The method of claim 76 wherein treating the polymeric layer to
reflow the polymer comprises using a technique selected from the group
consisting of thermal treatment, infrared treatment, microwave
30 treatment, RF treatment, mechanical treatment and solvent treatment.

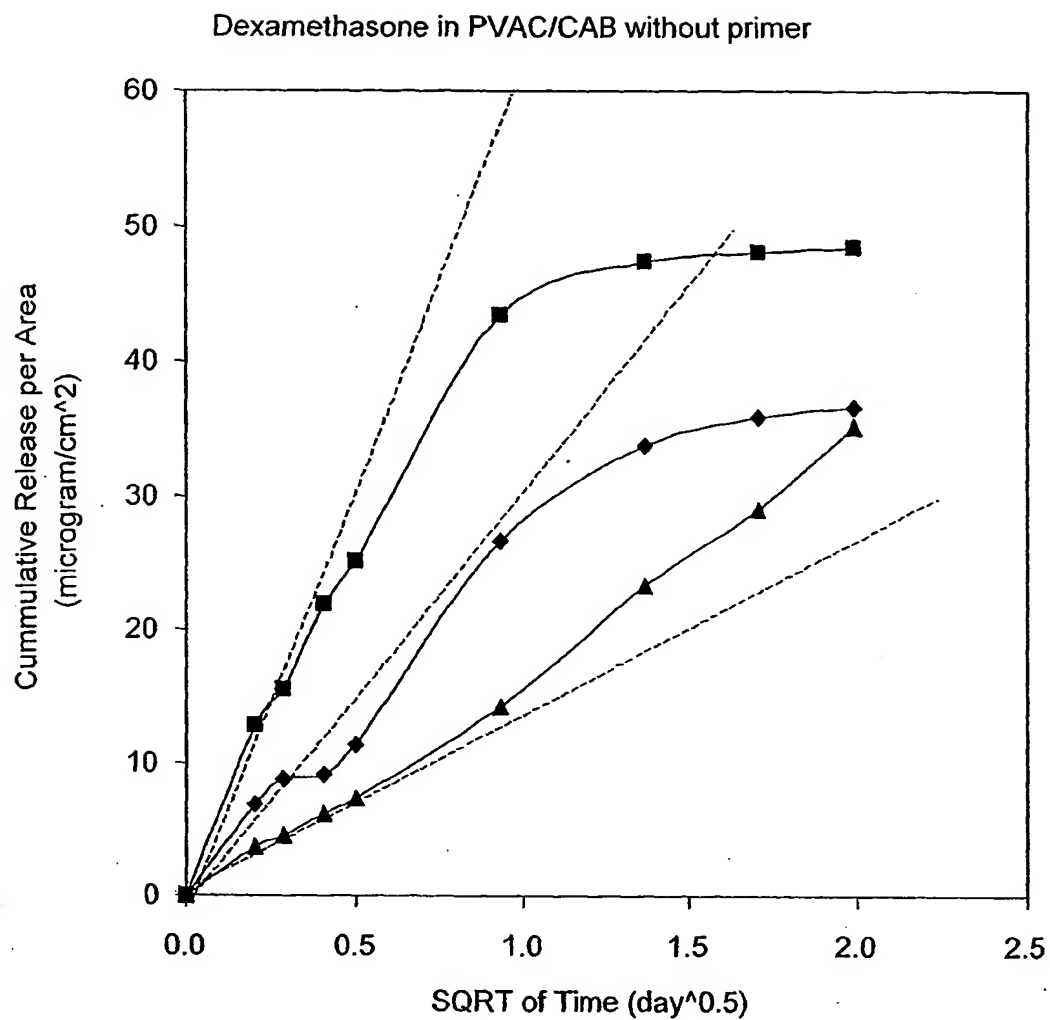
79. The method of claim 76 wherein treating the polymeric layer to
reflow the polymer comprises heating the polymeric layer to at least

about the melt flow temperature of the polymer for a time sufficient to reflow the polymer.

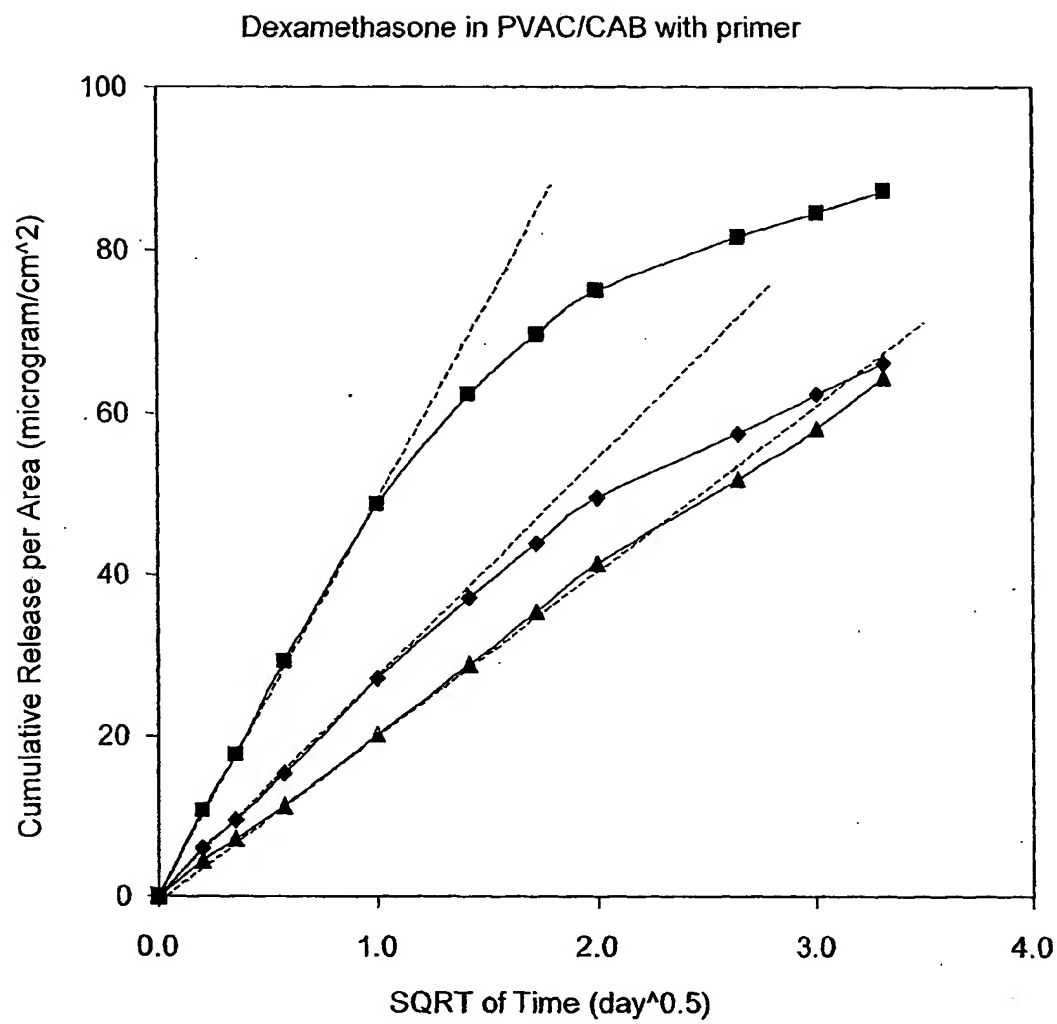
80. A method for delivering an active agent to a subject comprising:
- 5 providing a delivery device comprising
 a substrate surface; and
 a polymeric layer conformably adherent to the substrate
surface, wherein the polymeric layer comprises an active agent; and
 contacting the delivery device with a bodily fluid, organ or tissue
10 of a subject.

15

1/2

**FIG. 1**

2/2

**FIG. 2**

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 03/25463

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L31/02 A61L31/08 A61L31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 32474 A (STS BIOPOLYMERS INC ;WHITBOURNE RICHARD J (US)) 30 July 1998 (1998-07-30) page 5, line 1 - line 4 page 5, line 14 - line 16 page 8, line 1 - line 2; example 8 ---	1-3, 5-41, 45-80
X	WO 96 23601 A (SCHNEIDER USA INC) 8 August 1996 (1996-08-08) page 15, line 22 -page 16, line 2 page 16, line 6 - line 24; claim 1 --- -/-	1,3,6-8, 10, 20-22, 24-27, 45,71

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

16 December 2003

Date of mailing of the international search report

05/01/2004

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INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 03/25463

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 26281 A (CORDIS CORP) 4 April 2002 (2002-04-04) page 23, line 18 - line 32 page 25, line 1 - line 32; example 1 ---	1,3,5-7, 9,11, 13-17, 19-27, 45,71-80
X	ANONYMOUS: "Endoluminal stent with releasable radioisotope" RESEARCH DISCLOSURE, KENNETH MASON PUBLICATIONS, HAMPSHIRE, GB, vol. 447, no. 101, July 2001 (2001-07), XP002265301 ISSN: 0374-4353 page 4, paragraph 3 page 4 -page 5 ---	1,28,30, 40,41, 45,71
X	NISHI S ET AL: "Newly developed stent graft with micropored and heparin impregnated SPU film: Long-term follow-up study in vivo" INTERVENTIONAL NEURORADIOLOGY 2001 ITALY, vol. 7, no. SUPPL. 1, 2001, pages 161-166, XP009022986 ISSN: 1123-9344 page 162 -page 163 -----	1,28,30, 40,41, 45,71

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/25463

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 60-70, 80 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/US 03/25463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9832474	A	30-07-1998	US 5997517 A 07-12-1999
			CN 1250382 T 12-04-2000
			EP 0971753 A1 19-01-2000
			JP 2001509052 T 10-07-2001
			WO 9832474 A1 30-07-1998
			US 6306176 B1 23-10-2001
WO 9623601	A	08-08-1996	US 5919570 A 06-07-1999
			CA 2211643 A1 08-08-1996
			DE 69613104 D1 05-07-2001
			DE 69613104 T2 07-03-2002
			EP 0808223 A1 26-11-1997
			WO 9623601 A1 08-08-1996
			JP 3357064 B2 16-12-2002
			JP 10502855 T 17-03-1998
			US 6120904 A 19-09-2000
WO 0226281	A	04-04-2002	US 2001029351 A1 11-10-2001
			US 2002143386 A1 03-10-2002
			US 2002165608 A1 07-11-2002
			AU 1129902 A 08-04-2002
			AU 1132102 A 08-04-2002
			AU 7730201 A 11-04-2002
			AU 9316101 A 08-04-2002
			AU 9486901 A 08-04-2002
			CA 2357881 A1 29-03-2002
			CA 2424029 A1 04-04-2002
			CA 2424038 A1 04-04-2002
			CA 2424049 A1 04-04-2002
			CA 2425753 A1 04-04-2002
			EP 1192957 A2 03-04-2002
			EP 1335761 A1 20-08-2003
			EP 1322235 A1 02-07-2003
			EP 1322351 A1 02-07-2003
			EP 1322342 A1 02-07-2003
			JP 2002238994 A 27-08-2002
			WO 0226280 A1 04-04-2002
			WO 0226139 A1 04-04-2002
			WO 0226281 A1 04-04-2002
			WO 0226271 A1 04-04-2002
			US 2002094440 A1 18-07-2002
			US 2002111590 A1 15-08-2002
			US 2002133183 A1 19-09-2002
			US 2002051730 A1 02-05-2002
			CA 2408754 A1 22-11-2001
			EP 1280571 A1 05-02-2003
			WO 0187375 A1 22-11-2001
			WO 02078762 A1 10-10-2002
			US 2002193867 A1 19-12-2002
			WO 03000308 A1 03-01-2003